"Red Flags": Case Report of Cardiac Amyloidosis with Significant Coronary Artery Disease

Published online: 11 November 2024
https://doi.org/10.69944/pjc.0344b10d3c
https://pjc.philheart.org
ISSN: 0115-1029
e-ISSN: 2815-2123
Volume 52 Issue 2

Loren D.C. Gabayeron, MD | Cesar Antonio V. Zulueta, MD | Carlo Cortez, MD | Christie Anne Pabelico, MD | Allen Richard Villanueva, MD | Marianne Aludino, MD | Czarina Mae Reyes, MD
Perpetual Help Medical Center-Las Pinas

Correspondence:
Loren D.C. Gabayeron, MD
Email: lorengabayeron15@gmail.com

CONFLICTS OF INTEREST: None

Abstract

BACKGROUND: Cardiac Amyloidosis is a disorder of protein misfolding and metabolism in which insoluble fibrils are deposited in the myocardial extracellular matrix causing organ dysfunction and eventually death. It can exhibit cardiac signs and symptoms, or it can be identified through screening in patients who exhibit extracardiac symptoms of amyloidosis. As there were no clear clinical signs of cardiac amyloidosis and a biopsy is required to show amyloid deposition, the condition has been historically challenging to diagnose. Thus, a high index of suspicion based on the clinical presentation and the outcomes of the preliminary testing are crucial to determine the approach to diagnosis.

CASE SUMMARY: We outline a case of 75-year-old Filipino male who was admitted due to progressive exertional dyspnea. Cardiac Amyloidosis was considered due to evaluation findings of heart failure with preserved ejection fraction with restrictive type of cardiomyopathy. This was subsequently confirmed through extracardiac fat pad biopsy, echocardiographic strain analysis and Technetium (99mTc) Pyrophosphate (PYP) single photon emission computed tomography scan (SPECT).

CONCLUSION: This case report discussed the red flags of clinical manifestations of cardiac amyloidosis and highlighted the use of non-invasive diagnostic modalities to diagnose the disease. Cardiac amyloidosis remains a rare entity and with emerging therapies that have the potential to improve patient outcomes, early diagnosis is really important. Having high index of suspicion based on signs and symptoms can lead to early detection and an increased number of patients being referred for treatment.

INTRODUCTION

Cardiac Amyloidosis is a rare disease having a prevalence rate of around 1–2% in adults, increasing with age from 55-70 years.[1] It is indeed challenging to make a diagnosis as there is an inverse relationship between mortality and time of diagnosis. Given the advances in cardiovascular imaging techniques, conditions that were previously undiagnosed and thought to be uncommon are now being identified.

CASE PRESENTATION

We are presented with a 75-year-old male, hypertensive, diabetic for 20 years, known to have carpal tunnel syndrome and lumbar spine stenosis. History of present illness started one year prior to consult, when the patient started experiencing heart failure symptoms of shortness of breath, orthopnea and bipedal edema. Consult was done and transthoracic echocardiogram revealed mildly reduced left ventricular systolic function with global hypokinesia and moderate pericardial effusion. The patient was advised to undergo a coronary angiogram; however, he was not financially amenable at that time. Optimal medical therapy for heart failure was given however he was lost to follow-up. In the interim, the persistence of the abovementioned symptoms, particularly shortness of breath was noted, hence the consult.

The pertinent physical findings are as follows: stable blood pressure and heart rate, mildly tachypneic with adequate oxygenation, elevated jugular venous pressure levels, and cardiac

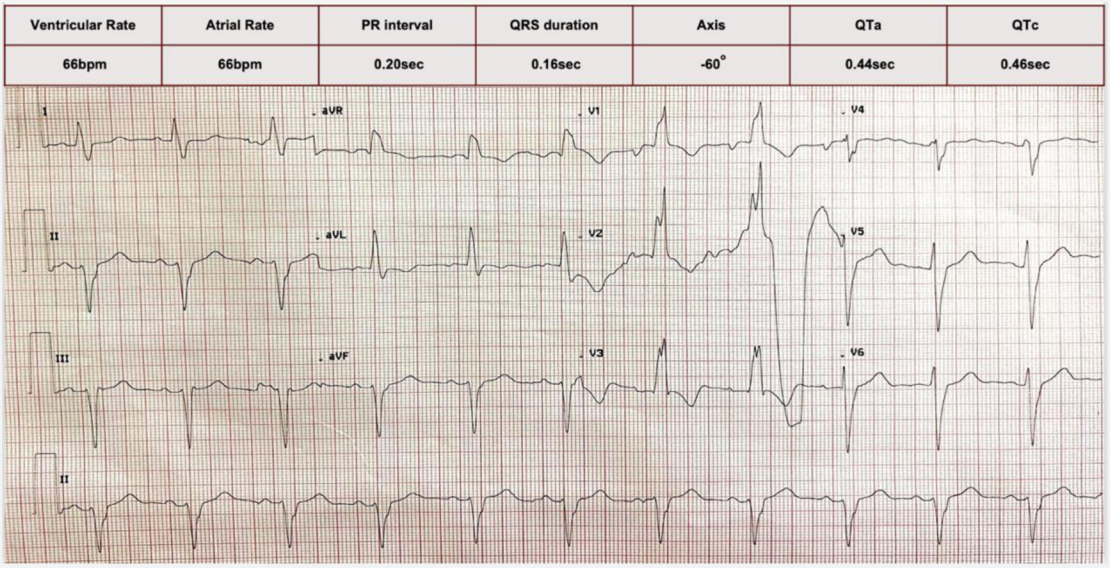

Figure 1. Electrocardiogram showing sinus rhythm, left atrial enlargement, bifascicular block

findings of grade 2 systolic murmur at the left parasternal area and at apex and grade 1 bipedal non-pitting edema. An electrocardiogram showed sinus rhythm, left atrial enlargement, bifascicular block, with complete right bundle branch block and left anterior fascicular block (Figure 1). Chest radiograph showed pulmonary congestive changes, cardiomegaly with pericardial effusion not ruled out, atheromatous aorta and osteodegenerative changes. High sensitivity troponin-I initially revealed 111.5ng/L which was decreased to 97.8ng/L the following day. NTproBNP was at 17, 504 pg/mL.

A repeat transthoracic echocardiogram showed mildly reduced ejection fraction with symmetrically hypertrophied left ventricular walls, global hypokinesia and severe diastolic dysfunction. Bi-atrial dilatation, pericardial effusion and the sparkling appearance of the myocardium were also noted. The global longitudinal strain with its corresponding bullseye map of the left ventricle shows the "cherry-on-top" sign which is typically seen in cardiac amyloidosis (Figure 2).

To rule out ischemic heart disease, coronary angiogram was done revealing significant lesion at the left anterior descending artery with 80% stenosis at its proximal segment. An incidental finding of coronary artery aneurysm at the proximal left anterior descending artery and left circumflex artery was also noted (Figure 3A).

Due to high index of suspicion for cardiac amyloidosis, patient was referred to hematology service and diagnostics were done such as serum free light chain assay which showed suspicious for low level monotypic serum free kappa light chains. Turbidimetry showed elevated free kappa light chain of 28.9mg/L, normal free lambda light chain at 21.7mg/L and an elevated kappa/lambda ratio at 1.33mg/L. A fat pad biopsy was done which showed amyloid dermal deposition (Figure 3B). To confirm the diagnosis of cardiac amyloidosis, a Technetium (99mTc) Pyrophosphate (PYP) single photon emission computed tomography scan (SPECT) was done which revealed a Grade 3 greater myocardial uptake than rib uptake. Quantitative analysis using Heart-to-Contralateral Lung (H/CL) ratio was calculated which showed 1.76 (positive value ≥1.5) (Figure 3C).

The management was focused on the treatment of symptoms arising from the heart failure and treatment of the underlying amyloidosis, which involves the use of agents that disrupt and facilitate clearance of deposited fibrils. The optimal heart failure medical therapy was continued and was started on Doxycycline and Ursodeoxycholic acid.

DISCUSSION

The term "amyloidosis" refers to the extracellular tissue deposition of highly ordered fibrils composed of low molecular weight subunits of a variety of proteins. [2] This may result in a wide range of clinical manifestations with respect to their type, location, and amount. [2]

Cardiac amyloid infiltration in the heart is referred to as "cardiac amyloidosis", which results to stiffening of the myocardium and is a rare form of cardiomyopathy. The most common types of cardiac amyloidosis, which account for 95 percent of the cases are transthyretin amyloidosis (ATTR amyloidosis) and light chain amyloidosis (AL amyloidosis).[3]

The clinical manifestations of amyloidosis varies depending on the pattern of organ involvement. Patients with light chain cardiac amyloidosis (AL amyloidosis) typically present at age ≥40 years and is a multisystem disorder which commonly affects the liver, kidneys, spleen, the autonomic and peripheral nervous systems, lungs, and heart. It usually occurs due to a plasma cell dyscrasia resulting in excessive production of immunoglobulin light chain units, with associated misfolding

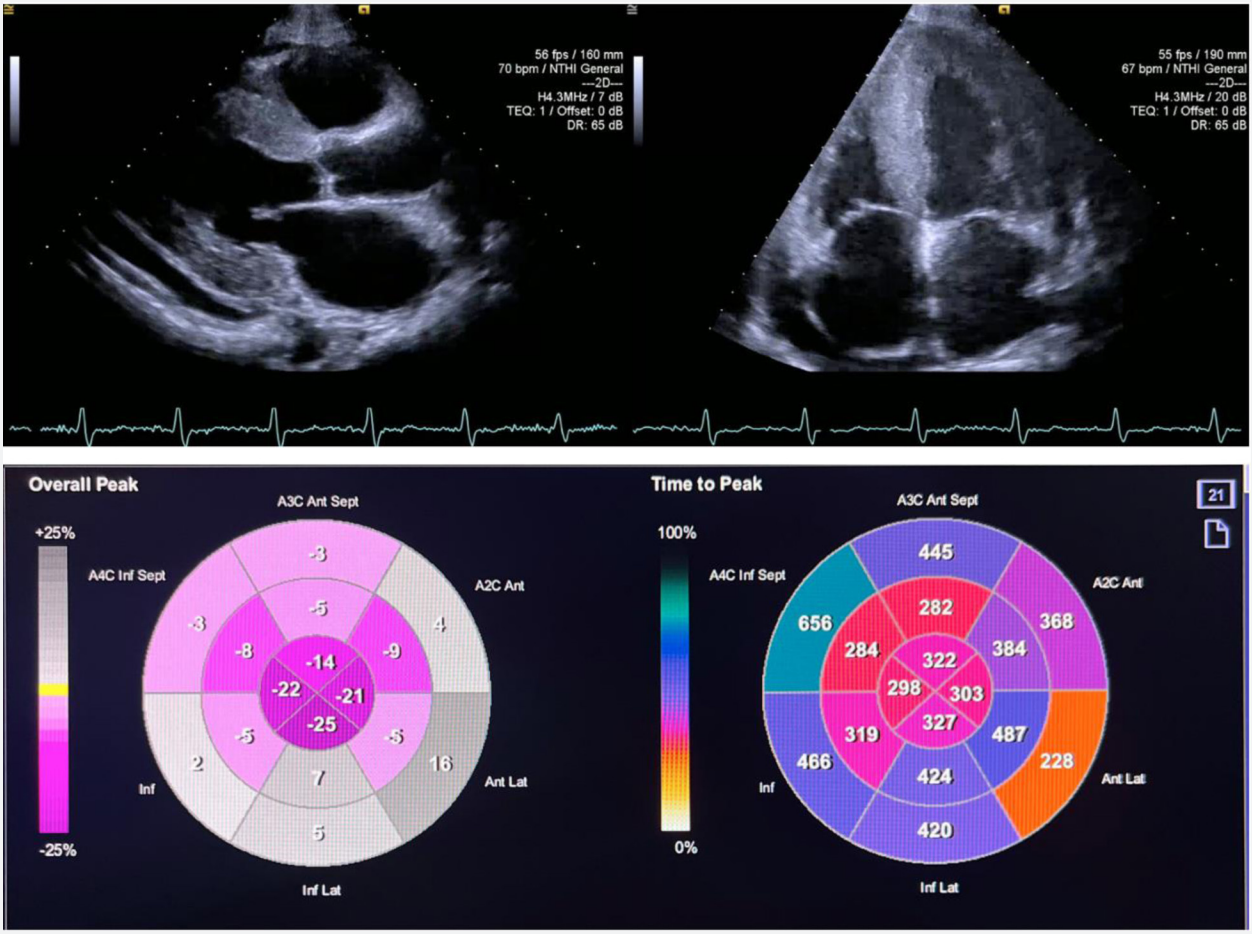

Figure 2. A. Transthoracic Echocardiogram showing concentric left ventricular hypertrophy, bi-atrial dilatation, moderate pericardial effusion. **B.** Global longitudinal strain showing "cherry on top" appearance

and deposition in extracellular tissue. Early diagnosis and initiation of treatment in may delay disease outcome although mortality remains high. [4] On the other hand, transthyretin cardiac amyloidosis (ATTR amyloidosis) typically present at age ≥60 years, and most commonly affects age group of >70 years. It occurs due to the misfolding of the liver derived precursor protein transthyretin. Two variants of this form are the hereditary form caused by mutations in the TTR gene and the wild type systemic senile amyloidosis. Peripheral neuropathy is one of the most common presentation of hereditary ATTR while the manifestations of wild type ATTR may include bilateral carpal tunnel syndrome and spinal stenosis for which may precede the cardiac complications.[4]

Congestive heart failure is the classic clinical presentation of cardiac amyloidosis. Symptoms of right ventricular failure may be more prominent in certain patients. These signs and symptoms are due to diffuse deposition of amyloid fibrils in the cardiac myocytes which causes significant thickening of both ventricles with associated stiffness, therefore results in impaired diastolic relaxation and the characteristic restrictive physiology. [2,4] Fibril deposition within the coronary vessels results in significant narrowing and may produce ischemia which may manifest as angina. [4] Symptoms of palpitations and syncope may be secondary to conduction abnormalities due to the direct toxicity of the fibrils to the cardiac myocytes and its conduction system. This may produce various degrees of heart block and atrial fibrillation is one of the most common identified arrhythmia. [2,4]

Initial workup for amyloidosis includes immunofixation, serum and urine electrophoresis, and immunoglobulin free light chains assay.[2] Serum and urine protein electrophoresis can be negative in half of the patients. Immunofixation and serum-free light chain are more sensitive tests. Serum free light chain immunoglobulin can be seen in >90 percent of the cases.[3] Definitive diagnosis requires histopathologic identification of amyloid with Congo red staining. Fat pad and bone marrow biopsy are both diagnostic. Although endomyocardial biopsy is the gold standard diagnostic test, hematology testing, fat pad, genetic testing, and bone marrow biopsies can aid in confirming the diagnosis without putting patients at risk for complications with endomyocardial biopsy. Biopsy of fat pad with Congo red staining has an overall sensitivity of 57 to 85 percent and a specificity of 92 to 100 percent.[4] Pro-BNP and troponin levels are typically elevated for it reflects vessel ischemia and myocyte

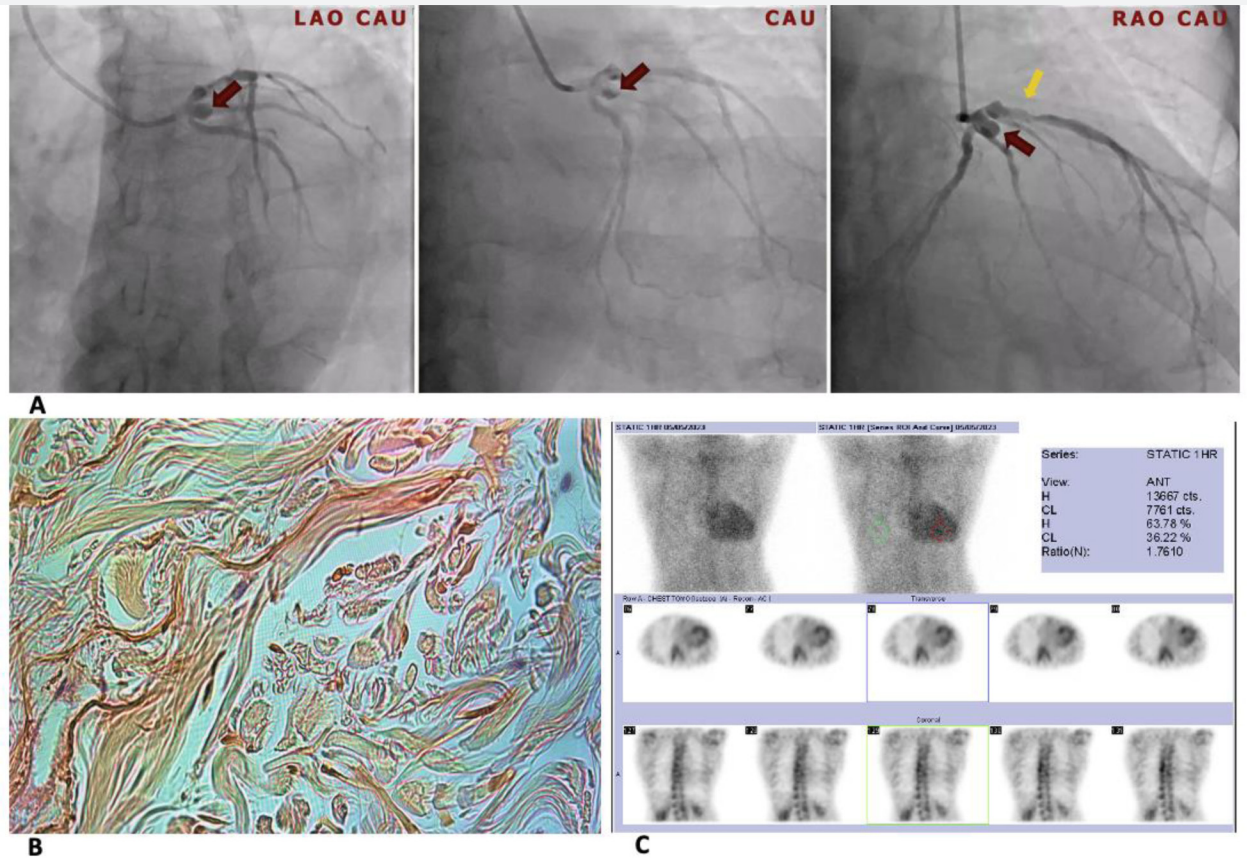

Figure 3. A. Coronary angiogram which showed a significant coronary artery disease of left anterior descending artery and a coronary artery aneurysm at the bifurcation of left main artery, left circumflex artery and left anterior descending artery; **B.** Fat pad biopsy with Congo red stain showing amyloid dermal deposition; **C.** 99mTc PYP SPECT showing grade 3 greater myocardial uptake than rib uptake.

injury.[6,7] Patients with age >65 years and heart failure along with a left ventricular wall thickness >12 mm at echocardiography are major criteria for the suspicion of cardiac amyloidosis. In addition, echocardiography shows mitral TDI velocity <5cm/s with grade 2 or worse diastolic dysfunction.[9] Strain analysis showing relative apical sparing with a "cherry on top" appearance seems to be the most sensitive and specific finding of amyloidosis.[8] This pattern of longitudinal strain alteration has high sensitivity (93 percent) and specificity (82 percent) for cardiac amyloidosis with proven utility in differentiating cardiac amyloidosis from other hypertrophic phenotypes.[8] Cardiac magnetic resonance imaging (CMRI) has an important role in the screening and evaluation of cardiac amyloidosis. CMRI may provide detailed tissue characterization of the myocardium and assessment of myocardial fibrosis. Late gadolinium enhancement (LGE) allows identification of silent myocardial infarction and provides important diagnostic information in specific cardiomyopathies. The typical finding for cardiac amyloidosis is a transmural or subendocardial pattern of late gadolinium enhancement (LGE).[6,7] Radionuclide imaging plays a unique role in the non-invasive diagnosis of cardiac amyloidosis. Using Technetium (99mTc) Pyrophosphate (PYP) single photon emission computed tomography scan (SPECT) can diagnose ATTR cardiac amyloidosis with high sensitivity of 99 percent and specificity of 86 percent.[6,7]

The management of cardiac amyloidosis is focused of the treatment of symptoms of heart failure and the treatment of underlying amyloidosis. Despite the belief that the guideline directed therapy for heart failure are not effective in transthyretin cardiac amyloidosis, there is a paucity of data on routine use of beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in ATTR.[1,6,10] Different treatment modalities for the clearance of amyloid deposits in tissue are under development in clinical trials. In AL amyloidosis, treatment is directed primarily at suppressing the underlying plasma cell dyscrasia. Novel therapies have been studied for hereditary transthyretin amyloid to reduce protein transcription.[1,6,10] These include the use of ribonucleic acid targeted therapies that interfere with hepatic TTR synthesis and other agents that reduce formation of transthyretin amyloid through stabilization of the tetramer configuration, preventing release of amyloidogenic monomers.[10]

Prognosis varies greatly depending on the stage of disease upon diagnosis and response to treatment. Prognosis is

assessed by a combination of biomarker risk assessment models and cardiac imaging. [1,6,10]

CONCLUSION

Cardiac amyloidosis is most commonly underdiagnosed. Detection of early cardiac amyloidosis, quantification of its burden, and assessment of response to therapy are important next steps for imaging to advance the evaluation and management of cardiac amyloidosis. Emerging therapies for cardiac amyloidosis increase the urgency for developing noninvasive imaging for early detection and for tracking therapeutic response.

This case highlights the clinical presentation and different diagnostic modalities that can be utilized to diagnose cardiac amyloidosis. Having high index of suspicion based on signs and symptoms can lead to early detection and increased number of patients being referred for treatment.

An informed consent has been obtained from the involved patient and have given approval for the following information to be published. The data collected in this study was kept anonymized and confidential.

This case report declares that it involves minimal risk to subjects and will not adversely affect the patient's rights and welfare.

The primary investigator declares no conflicts of interest to disclose.

REFERENCES

1. McDonagh T.A., Metra M., Adamo M., Gardner R.S., Baumbach A., Böhm M., et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* 2021;42:3599–3726. doi: 10.1093/eurheartj/ehab368.
2. Falk RH, Alexander KM, Liao R, Dorbala S., et al. AL (Light-Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy. *J Am Coll Cardiol* 2016; 68:1323.
3. Maleszewski JJ. Cardiac amyloidosis: pathology, nomenclature, and typing. *Cardiovasc Pathol* 2015; 24:343-350 [PMID: 26361138 DOI: 10.1016/j.carpath.2015.07.008]
4. G. Merlini, A. Dispenzieri, V. Sanchorawala et al., "Systemic immunoglobulin light chain *amyloidosis," Nature Reviews Disease Primers*, vol. 4, no. 1, 2018.
5. Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *JACC Heart Failure.*2019;7:709–716.
6. Donnelly JP and Hanna M. Cardiac amyloidosis: An update on diagnosis and treatment. *Cleve Clin J Med* 2017; 84: 12-26 [PMID: 29257735 DOI: 10.3949/ccjm.84.s3.02]
7. M. Rosenzweig and H. Landau, "Light chain (AL) amyloidosis: update on diagnosis and management," *Journal of Hematology and Oncology*, vol. 4, no. 1, 2011.
8. D. Phelan, P. Collier and P. Thavendiranathan. "Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis," *Heart*, vol. 98, no. 19, pp. 1442–1448, 2012.
9. Theresa A McDonagh, Marco Metra, Marianna Adamo & Roy S Gardner, et al. ESC Scientific Document Group , 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the *ESC, European Heart Journal*, Volume 42, Issue 36, 21 September 2021, Pages 3599–3726, https://doi.org/10.1093/eurheartj/ehab368
10. Dohrn MF, Ihne S, Hegenbart U, et al. Targeting transthyretin-Mechanism-based treatment approaches and future perspectives in hereditary amyloidosis. *J Neurochem* 2021; 156:802.